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INCIDENCE OF MUCOSITIS IN PATIENTS UNDERGOING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION AT A SINGLE CENTER

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ABSTRACT

Goal: The aim of this study was to describe the incidence of oral mucositis (OM) in patients undergoing autologous hematopoietic stem cell transplantation (auto-HSCT), relating it to the main clinical factors. Methodology: Descriptive analysis based on a randomized clinical study was conducted with patients undergoing HSCT at the University Hospital of Federal University of Juiz de Fora between January 2018 and June 2019. The World Health Organization oral toxicity scale was used to assess the degree of oral mucositis and adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 version. Results: Thirty-eight patients were evaluated. The incidence of OM and severe oral mucositis (SOM) was 57.9% and 21.0%, respectively. The mean duration of OM was 7.2 ± 2.6 days and the lomustine, etoposide, cytarabine and cyclophosphamide protocol (LEAC) presented the longest mean time 8.1 ± 3.1 days (p-value 0.02). The number of viable CD34+ cells and the onset day of neutropenia were predictors of SOM. Conclusion: The incidence of OM in patients undergoing HSCT was lower than reported in the literature, being more severe in patients who received less CD34+ cells and in patients with early onset of neutropenia.

Keywords: hematopoietic stem cell transplantation; mucositis; risk factors

INTRODUCTION

Mucositis is the most frequent consequence of antineoplastic drugs toxicity during Hematopoietic Stem Cell Transplantation (HSCT), resulting in changes in patients 'oral microbiota and a significant impact on their quality of life [1, 2, 3, 4, 5]. Different levels mucositis grade and its incidence were described by Bashir *et al.* (2019) [6] in patients with multiple myeloma underwent auto-HSCT who had the conditioning regimen with melphalan alone replaced by busulfan plus melphalan.

Inflammatory lesions in the gastrointestinal mucosa characterize mucositis and its pathophysiology involves a complex process of molecular and cellular events that include five phases: initiation, primary damage response, amplification, ulceration and healing [7, 8].

The occurrence of fever and infection is related to mucosal barrier injuries. Different studies often show the fever as a consequence of neutropenia, however, lesions on mucosal barrier also leads to infections. Considering the infections after the chemotherapy protocol for HSCT lesions of the mucous barrier are more important than neutropenia, and should therefore be carefully evaluated [9, 10]. Mucositis affects the patient´s nutritional status and is related to parenteral nutrition recommendation, the use of opi-

oids, as well as the increase in hospitalization time and costs [11, 12]. Patients undergoing HSCT who developed a high degree of mucositis according to oral mucositis assessment scale (OMAS) resulted in a 45% increase in hospital costs [11].

Nutrition has an important role on health maintenance and either mucositis and malnutrition (in many cases related to mucositis) compromise the nutritional status of patients. The prevalence of malnutrition is over 75% among children and adolescents with cancer [13].

In 2014, a systematic review was published to update the Clinical Practice Guidelines of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC / ISOO). The recommended intervention therapies with level I or II evidence consisted of: cryotherapy, recombinant human keratinocyte growth factor-1 (KGF-1/palifermin), low intensity laser therapy (wavelength at 650 nm, power of 40 mW, and energy dose of 2 J / cm2), mouthwash with benzidamine [14].

Therefore, the aim of this study was to determine the incidence and clinical impact of mucositis in patients undergoing auto-HSCT, relating them to the main clinical factors.

PATIENTS AND METHODS

A descriptive analysis based on a randomized clinical study was carried out with patients submitted to HSCT at the University Hospital of Federal University of Juiz de Fora (HU-UFJF) between January 2018 and June 2019. All participants signed a free and informed consent. This study was previously approved by the Human Research Ethics Committee of the HU-UFJF and the ethical principles were in accordance with Declaration of Helsinki on human subject research.

This study included all patients admitted to the HSCT Unit of HU-UFJF from January 2018 to June 2019 for the auto-HSCT who had not yet started the conditioning phase. Following the protocol used at the HSCT Unit, all the patients were submitted to laser therapy to prevent mucositis. In summary, the protocol consists of prophylactic low-level scanning therapy with 1J/cm2 (600-690 nm) from the first day of conditioning until hospital discharge and, in case of lesions, direct application to the area with 2J/cm2 (790-830 nm).

The conditioning protocol used for patients diagnosed with multiple myeloma was melphalan (Mel) 200 mg/m2 and Mel 140 mg/m2 for those age >65 years. For patients with Hodgkin lymphoma or non-Hodgkin lymphoma, the protocol was CBV (cyclophosphamide 6 mg/m2, carmustine 300 mg/m2, and etoposide 1200 mg/m2) or LEAC (lomustine 300 mg/m2, etoposide 1000 mg/m2, cytarabine 4000 mg/m2, and cyclophosphamide 5400mg/m2 and LEC (lomustine 200 mg/m2, etoposide 1000 mg/m2, cyclophosphamide 6000 mg/m2).

Mucositis was evaluated according to the oral toxicity scale of World Health Organization (WHO) and is described in table 115. The evaluation period of the patients was from the first day of conditioning chemotherapy until the day of the end of neutropenia. Each patient was categorized according to the highest level reached during this period. Oral mucositis grade equal or higher to 3 was classified as SOM.

This study included the relationship between the number of stem cells, characterized by the expression of CD34, received by the patient in the auto-HSCT with the incidence of OM.

The National Cancer Institute criteria version 4.0 was used for grading of adverse events (AEs) during the study. The AEs evaluated were nausea, emesis, dysphagia, dyspepsia, diarrhea, and xerostomia.

The collected data were analyzed using R Commander program. Categorical data was described using frequencies and percentages and associations with OM were verified by the C2 test or Fisher's exact test. The collected data were analyzed using R Commander program. Categorical data was described using frequencies and percentages and associations with OM were verified by the C2 test or Fisher's exact test. Quantitative data were presented using means, medians, SDs, ranges, and univariate analysis, performed with the t test or Mann–Whitney test. The statistical tests were two-sided at a significance level of 5%.

RESULTS

Thirty-eight patients submitted to the auto-HSCT were evaluated in the period and 57.9% of them were male. The average age was 53 years, ranging from 18 to 70 years. The characteristics of the patients included in this study are shown in Table 2.

The number of days in neutropenia varied between 6 and 15 days with an average of 9.3 ± 2.0. The neutropenia was started between D-2 to D+6 with an average of 3.0 ± 2.2 days, whereas the end varied between D+9 ± D+13 and an average of 11.2 ± 1.0.

More than half of the patients had some degree of OM (57.9%;n = 22) and 36.4% of them had SOM (Figure 1).

Regarding the duration of OM was observed an average of 7.2 ± 2.6 days (D+ 3 - D+ 14.0). The beginning of OM signs occurred on average at 4.4 ± 2.5 days, varying between D-2 and D+8, and day D+5 the symptoms appeared in most of patients. The end of OM occurred in an average of 10.6 ± 1.1 days (D+8 – D+13), with a median of 11.0 days.

Comparing the mean days of OM in patients submitted to different chemotherapy conditioning protocols the following results were determined: MEL (3.2 days ± 3.5), CBV (2.0 ± 4.0), LEAC (8.1 ± 3 , 1), LEC (5.7 ± 5.5) p-value 0.020 (Figure 2).

The average length of stay in the hospital without OM was evaluated and no statistically significant difference was found (p = 0.203) among the chemotherapy protocol groups (Figure 3).

Based on multivariate analysis, the incidence of SOM (21.0%) was related to the number of CD34+ cells/kg infused as well as the day of the beginning of neutropenia, as shown in Table 3. Other variables evaluated were gender, age, diagnosis, chemotherapy conditioning protocol, neutropenia duration and body mass index prior to treatment and none of these had influence on the incidence of SOM.

DISCUSSION

The incidence of OM in patients undergoing auto-HSCT with different conditioning protocols assessed during a 17–month period between 2018 and 2019 is describe in this article.

The use of laser therapy is recommended for prevention and treatment of OM and several parameters must be considered as wavelength (nm), power (mW), amount (J/cm2)and rate (mW/cm2) of energy supplied to the tissues and time of application(s)16. The laser protocol applied in this study is in accordance with the MASCC/ISOO Clinical Practical Guidelines for The Management of Mucositis Secondary to Cancer Therapy [17].

The neutropenia duration was approximately 9 days, similar to the previously work performed by our group (2017) [18], in which a nutritional supplementation was applied to patients undergoing HSCT and shows overall mean duration of neutropenia of 9.87 days varying 6.80 days.

In this work was observed a lower incidence of OM in comparison to studies previously reported in the scientific literature. The occurrence of OM was identified in 60.7% of patients submitted to HSCT 18. [20] reported that treatment-related mucositis affects over 75% of patients undergoing HSCT. Chaudhry *et al.* (2016) [7] systematically reviewed the incidence and severity of OM in patients undergoing allogeneic HSCT and found that 73,2% of patients (total of patients equal to 395 in 8 myeloablative regimen studies) exhibited OM of any degree. A total of 9.5% of the patients experienced OM grade 1 and 79,7% of the patients showed OM between grades 2 and 4.

The begging of OM symptoms usually starts at the end of the conditioning regimen or 4 days later according to the literature [21, 22]. Many studies show that OM average duration varies from 5 to 9 days (maximum of 12 days) in patients undergoing allogeneic HSCT23-26. Patients supplemented with whey protein concentrate during a study to prevent OM presented mean duration of mucositis of 8.4 ± 3.50 days (minimum of 3 and maximum of 16) in the group with a lower dose of supplementation and 7.0 ± 3.4 days (minimum of 4 and a maximum of 17) in the group with a higher dose18.

The conditioning chemotherapy had higher correlation to the incidence and grade of OM compared to patients age. The incidence of SOM was higher in patients submitted to administration of busulfan plus cyclophosphamide as a conditioning regimen when compared to other protocols [19].

Comparative analysis for incidence of OM among researches depends on the chemotherapy applied protocols. Studies show that the conditioning protocol has an impact on the evolution of OM 6, 19. However, in this study, the incidence of mucositis was not correlated to the chemotherapy applied protocols applied. Thus, it was possible to compare the incidence of mucositis among all patients. Although, we observed that the duration of mucositis was longer in patients undergoing the LEAC protocol.

Fleming *et al*. (2014) [27] found no correlation between the amount of stem cells received by patients and the incidence of mucositis in patients submitted to auto-HSCT. However, in the present study, we found that the amount of stem cells infused was inversely proportional to the incidence of SOM. Therefore, we conclude that the number of stem cells infused into the patient in the auto-HSCT as well as the day of onset of neutropenia are predictors of the incidence of severe mucositis.

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Table 1 - World Health Organization Oral Mucositis Classification

SCALE	0	1	2	3	4
Oral toxicity scale (WHO)	No alterations	Pain, sensibility and erythema	Erythema and ulcers, able to swallow solid foods	Ulcers (liquid diet only)	Ulcer, extensive mucositis (unable to feed)

Source: World Health Organization Oral15

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